REMARKS/ARGUMENTS

Applicant hereby responds to the office action of July 17, 2008.

Claims 5 and 11 have been amended to include "an effective amount of " thiocyante.

Claim 10 has been amended to delete the word "infection"

Claim 19 has been amended to recite that the hydrogen peroxide is an "aerosol". Support for this amendment can be found in at page 4, line 4 through page 5 line 32.

No new matter is added by the Amendments.

I. Response to the Objection to Claim 26

Claim 26 stands objected to under 37 C.F.R. § 1.75(c) as allegedly having improper dependent form. Claim 10 has been amended to delete the term "infection". It is believed that the objection to claim 26 is now moot in view of the amendment.

II. Response to Claim Rejections under 35 U.S.C. § 102 (e)

Claims 19 and 27-28 stand rejected under 35 U.S.C. § 102(e) as being anticipated by United States patent number 6,589,481 to Lin ("Lin").

35 U.S.C. § 102(e) provides in relevant part:

A person shall be entitled to a patent unless:

> (e) the invention was described in - (1) an application for patent, published under **section 122(b)**, by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in **section 351(a)** shall have the effects for the purposes of this subsection of an application filed in the United States only if the

international application designated the United States and was published under **Article 21(2)** of such treaty in the English language; or

Applicant asserts that Lin as a matter of law cannot anticipate the invention of claims 19 or 27-28 as the devices disclosed in Lin are not inhalers as that term is well known and understood in the art. Lin is directed to sterilization of devices using hydrogen peroxide and plasma preferably in a vacuum. Example 1 of Lin is a nebulizer.

Inhalers are well known in both the art and to the consumer and are distinguished in the art from nebulizers. See The Mayo Clinic web page on Asthma Inhalers at http://www.mayoclinic.com/health/asthma-inhalers/HQ01081, a copy of which is attached hereto as Exhibit 1 which provides in relevant part:

> If you're unable to use an inhaler, a nebulizer may be an option. Nebulizers are designed for those who can't use an inhaler, such as infants, young children and those who are seriously ill. The device works by converting medication into a mist and delivering it through a mask that you wear over your nose and mouth.

Similarly, Web MD provides and Asthma Guide published on the web at http://www.webmd.com/asthma/guide/asthma-inhalers which shows inhalers as metered dose inhalers and dry powder inhalers. Nebulizers are not included in the category of inhalers.

Lin does not teach the use of an inhaler, nor the use of hydrogen peroxide aerosol in an inhaler.

Claim 19 has been amended to specifically recite that the hydrogen peroxide is aerosolized.

Further, none of the devices disclosed in Lin are suitable for administration of an aerosol of hydrogen peroxide. Examples 1 and 2 deliver liquid, not a hydrogen peroxide aerosol, into the lumen of a nebulizer. The other examples are not capable of administering aerosols to a patient.

Claim 27 and 28 depend from claim 19 and are not anticipated by Lin for the reasons that claim 19 is not anticipated by Lin. Further claim 27 limits the concentration of hydrogen peroxide.

Lin also teaches that hydrogen peroxide alone was not effective in sterilizing instruments except at a 12% concentration and then only after soaking for 90 minutes. Lin if anything clearly teaches away from claim 27 by stating:

> "It is clear from these data that contact with dilute hydrogen peroxide solution alone is ineffective at providing sterilization , unless extended soak times and concentrated solutions are used." column 8, lines 17-20.

In fact, the working examples of Lin used 59% hydrogen peroxide, whereas the desired concentration in the lungs of the present invention at 10^{-7} to 10^{-4} M is orders of magnitude lower.

Applicant asserts that claims 19, 27 and 28 are not anticipated by Lin and are allowable.

II. Response to Claim Rejections under 35 U.S.C. §112, First Paragraph.

Claims 1-2, 4-11, 18 and 21-26 stand rejected under 35 U.S.C.§ 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicant asserts that the present specification as drafted is enabled and fully complies with the factors set forth under *In re Wands*, 858 F.2d 731; 8 USPQ2d 1400 (Fed. Cir.. 1988).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any

experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

The applicant asserts that the present claims are enabled in the description.

Applicant hereby addresses the Wands factors in the order presented by the Office Action.

Breadth of Claims

Applicant agrees with the examiner that the claims are relatively broad. Claim 1 and its dependent claims 2-9 and 21 are limited to the treatment symptoms of cystic fibrosis. Claim 10 and its dependent claims 11, 18 and 22-26 are limited to treating a lung infection in a mammal.

Nature of the Invention/State of The Prior Art

The Examiner has summarized the prior art in the office action including references to two MSDSs which show high levels of hydrogen peroxides are dangerous. Applicant has provided specific guidance as to the concentrations of hydrogen peroxide desired in the lungs with the target being 10^{-7} to 10^{-4}. The examiner has effectively noted that the exposure of the lungs to hydrogen peroxide levels of 3% are quite safe as evidenced by the MSDS for 3% hydrogen peroxide and the toxicology literature cited. The applicant's claimed ranges are orders of magnitude below a 3% level.

Similarly, the MSDS for thiocyanate does not negate enablement of the claims as to administration of thiocyanate. The specification provides pharmacologically effective target concentrations in the lungs which are extremely small. These concentrations provide a clear teaching to one of skill in the art. Further, the enablement of the administration of thiocyanate was already acknowledged by the Patent Office in the parent application which issued as patent number 6,702,998. Applicant has amended claims 5 and 11 to recite an "effective amount of thiocyanate"

The office action points to Conner et al, FEBS Letters, Vol 581, 271; pp274, Fig. 3 s supporting a presumption that the present invention is not enabled because the "addition of LPO or hydrogen peroxide in the absence of added SCN^- **to washes from cultured secretions from cystic fibrosis (CF) lungs was unable to restore antibacterial activity in CF cultures** and only non-CF cultures showed antibacterial activity upon addition of LPO or hydrogen peroxide." Office action, page 6, (emphasis in original).

However, this statement does not reflect the full teachings of the reference which also states:

> "In our studies shown here, and in previous studies [12], small numbers of bacteria were used in an in vitro system that was not replenished with either SCN^- or H_2O_2 during the assay. In vivo, continuous production of H_2O_2 [18,36,49] and SCN transport in the presence of LPO are expected to continuously produce larger quantities of $OSCN^-$ for antibacterial host defense that are expected to prevent colonization of the airway but may not e able to eradicate an established infection."
>
> Conner at 276.

The in vitro data in Fig 3 does not show unpredictability, but rather shows limitations of an in vitro system used for testing. As noted above, in an in vivo system, a supply of SCN^- is present. In some situations, as contemplated by the claims, supplementation with additional may be required.

Similarly the teachings that LPO antibacterial activity is known to depend on concentration of hydrogen peroxide, thiocyanate and bacteria in Wijkstrom-Frei cited by the examiner also does not show unpredictability to negate enablement as the art teaches these are provided in vivo systems.

Level of One of Ordinary Skill & Predictability /Unpredictability in the Art.

The Examiner has properly noted that the level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees. Applicant however disagrees that there is a lack of predictability with respect to the identifying dose ranges and formulations.

Delivery of medications via inhalers is well known in the art as cited in the specification. The courts have upheld enablement upon identification of a molecule in a specification despite the absence of specific dosages. See ?*In re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981). In contrast, the present application teaches a desired concentration of hydrogen peroxide in the lungs.

Guidance/Working Examples

Applicant has provided target ranges for concentration of hydrogen peroxide and for thiocyanate in the fluid in the lungs. The examiner has noted that one of skill in the art is high skilled possessing advanced degrees. It is well within the skill of a pharmacologist and a formulation chemist to devise a formulation suitable for reaching these target ranges as part of a normal development drug process as this is routinely performed during the development of any drug. The active agent which is central to the present claims, hydrogen peroxide, is very well characterized and understood as evidenced by the MSDS cited by the examiner. There is nothing in the record which suggests undue experimentation will be required.

Applying the Wands factors it is clear that there is very high skill in the art. It is also clear that while the claims are relatively broad, so is the teaching within the specification. The cited art teaches the roles of hydrogen peroxide and thiocyanate in treating infections in the lung. Applicant asserts that claims 1-2, 4-11, 18 and 21-26 are in fact enabled. A person of skill in the art following the teachings of the present specification would be able to formulate hydrogen peroxide in an inhaler and determine the amount of drug to be delivered to achieve the desired pharmacologic levels taught in the specification.

III. Response to Claim Rejections under 35 U.S.C. §112, Second Paragraph.

Claims 9, 18 and 27 stand rejected under 35 U.S.C. §112, second paragraph for allegedly failing to point out and distinctly claim the subject matter which the applicant regards as the invention. Examiner contends that the recitation of a Molar concentration in the lungs is

indefinite because a concentration is not indicative of an amount. Pharmaceutical patents routinely claim pharmacological parameters such as concentration and it is well within the purview of one of skill in the art to calculate a dose based on known physiological properties or to determine dose based on routine empirical testing such as the conduct of dose ranging studies.

IV. Double Patenting

Applicant believes the present double patent is premature as there are no allowed claims. Applicant will file a terminal disclaimer in the future when the double patenting rejection can be evaluated against claims which are otherwise allowable but for the double patent rejection.

III. Conclusion

Applicants submit that these amendments and remarks, when entered, place the claims in condition for allowance and respectfully request that the Examiner reconsider the application in light of these amendments and all claims in the subject application be permitted to proceed to allowance.

Applicant's attorney will be at the Patent Office on Friday November 21 and requests a meeting with the examiner if possible after 4 pm on that date.. In the event such a meeting is not possible, applicant's attorney requests a telephonic interview with the Examiner to discuss any remaining issues.

Dated: November 17, 2008

By: _____

Michael J. Keller
USPTO Reg. No. 38,201

LOTT & FRIEDLAND, P.A.
One East Broward Blvd.
Suite 1609
Fort Lauderdale, Florida 33301
Telephone: (954) 315-5044

EXHIBIT 1

Mayo Clinic Web Page
Asthma Inhalers
http://www.mayoclinic.com/health/asthma-inhalers/HQ01081

ASTHMA

Nov 14, 2008

Asthma inhalers: Which one's right for you?

Inhalers allow people with asthma to lead active lives without fear of an attack. Here's a rundown of inhaler types, with tips on proper use.

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Inhalers have transformed asthma treatment. They enable children and adults with asthma to deliver medicine directly to their lungs nearly anytime and anywhere. A variety of inhalers are available to help relieve or control asthma symptoms.

Types of inhalers

Inhalers are hand-held portable devices that deliver medication directly to the lungs. A variety of inhalers exist, but they basically fall into two categories:

Metered dose inhalers

These inhalers use a chemical propellant to force a measured dose of medication out of the inhaler. They consist of a pressurized canister containing medication, a mouthpiece and a metering valve that dispenses the correct dose of medication. The medication is released either by squeezing the canister or by inhaling. You may find it easier to use a hand-actuated inhaler with a spacer — a short tube that attaches to the inhaler. Using a hand-actuated inhaler to release the medication into the chamber gives you time to inhale more slowly. It decreases the amount of medicine that's deposited on the back of your throat and increases the amount that ultimately reaches your lungs.

Some metered dose inhalers have counters so that you know how many doses remain. If there is no counter, you have to track of the number of doses you've used so that you know when the inhaler is out of medication.

The chemical propellant in metered dose inhalers has traditionally been a chlorofluorocarbon (CFC). But after an international agreement to ban CFCs because they damage the ozone layer, other propellants such as hydrofluoroalkane (HFA) are now used instead. The dose of medication released by an HFA inhaler may feel softer and warmer than the dose released by a CFC inhaler. If you're used to a CFC inhaler, it may not seem like a complete dose — even though the medication is reaching your lungs.

Dry powder inhalers

These inhalers don't use a chemical propellant to push the medication out of the inhaler. Instead, the medication is released by breathing in more quickly than you would with a traditional metered dose inhaler.

Some people find dry powder inhalers easier to use than the conventional pressurized metered dose inhalers because hand-lung coordination isn't required. Some models require operating a cocking device that requires dexterity. Available types include a dry powder tube inhaler, a powder disk inhaler and a single-dose dry powder disk inhaler. Spacers shouldn't be used with dry powder inhalers.

Comparing inhaler types

Choosing the right kind of inhaler for you depends on several factors, such as your hand-breath coordination, your dexterity, whether you can take a deep, fast breath, and what types of medication you need. The chart below can help you understand the pros and cons of each type. Work with your doctor to find the best inhaler for your needs.

Inhaler features

Metered dose inhaler	Metered dose inhaler with a spacer	Dry powder inhaler
Portable and convenient	Less portable and convenient, more complex and more expensive than	Portable and convenient

	a metered dose inhaler without a spacer	
Doesn't require a deep, fast breath	Doesn't require a deep, fast breath	Requires a deep, fast breath
Accidental exhalation before activation won't disrupt medication	Accidental exhalation before activation won't disrupt medication	Accidental exhalation before activation will blow away medication
Hand-actuated models without a spacer require hand-breath coordination	Hand-breath coordination is not critical	Hand-breath coordination is not necessary
Can result in large amounts of medication on the back of your throat and tongue	Less medication settles on the back of your throat and tongue	Can result in large amounts of medication on the back of your throat and tongue
Minimal or no maintenance required	Spacer requires periodic cleaning with soap and water	Minimal or no maintenance required
Some models require you to keep track of how many doses remain	Some models require you to keep track of how many doses remain	It is clear when the device is out of medication
Requires shaking and priming	Requires shaking and priming, correct use of spacer	Single-dose models require loading capsules for each use
Humidity does not affect medication	Humidity does not affect medication	High humidity can cause powdered medication to clump

Medications delivered through inhalers

Inhalers are used to deliver a variety of asthma medications — some that assist with long-term control and others that provide quick relief of symptoms. Some medications may only be available in certain inhaler types. Inhaled asthma medications include:

- **Short-acting bronchodilators.** These medications, including albuterol (Proventil, Ventolin) and pirbuterol (Maxair), provide immediate relief of asthma symptoms.
- **Long-acting bronchodilators.** These medications relieve asthma symptoms for longer periods of time. They include salmeterol (Serevent) and formoterol (Foradil).
- **Corticosteroids.** Used long term to prevent asthma attacks, these medications include beclomethasone dipropionate (Qvar), fluticasone (Flovent), budesonide (Pulmicort), triamcinolone acetonide (Azmacort) and flunisolide (Aerobid).
- **Cromolyn or nedocromil.** These nonsteroidal medications are used long term to prevent inflammation.
- **Corticosteroid plus long-acting bronchodilator.** This medication combines a corticosteroid and a long-acting bronchodilator (Advair, Symbicort).

Inhalers may come with slightly different instructions. Follow those instructions carefully and ask your doctor for a demonstration.

MORE ON THIS TOPIC

- Video: How to use a metered dose asthma inhaler and spacer
- Video: How to use a dry powder tube inhaler
- Video: How to use a dry powder disk inhaler
- Video: How to use a single-dose dry powder inhaler

The importance of using inhalers properly

It's important that you use your inhaler correctly so that the medication reaches your lungs. Carefully follow the instructions. And ask a doctor, nurse or pharmacist for a demonstration. Use the inhaler in front of this person and ask for feedback. Then practice at home in front of a mirror.

If you're unable to use an inhaler, a nebulizer may be an option. Nebulizers are designed for those who can't use an inhaler, such as infants, young children and those who are seriously ill. The device works by converting medication into a mist and delivering it through a mask that you wear over your nose and mouth.

Using an inhaler is just one part of your asthma treatment plan, which may also include checking your lung function with a peak flow meter, eliminating asthma triggers and exercising. But knowing what types of inhalers are available and how to use them can help you better manage your asthma and get the most from your treatment.

MORE ON THIS TOPIC

- Asthma medications: Know your options
- Asthma in adults: Gain control with a written plan

RELATED

- Asthma medications: Know your options
- Prednisone and other corticosteroids: Balance the risks and benefits
- Video: How to use a dry powder tube inhaler
- Video: How to use a dry powder disk inhaler
- Video: How to use a single-dose dry powder inhaler
- Video: How to use a metered dose asthma inhaler and spacer

By Mayo Clinic Staff
Aug. 17, 2007

HQ01081